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Crystallographic screening of sp3-rich fragment library for Protein Kinase A

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Over the last two decades, fragment-based lead discovery has resulted in two approved drugs and to more than 30 drugs in clinical trials1. One of the strengths of the fragment-based approach is the efficient sampling of the chemical space using small organic molecules with MW usually below 250 Da.

Established screening libraries have been designed by combinatorial chemistry. The resulting profile of such libraries is dominated by sp2-carbons and aromatic rings, which undermines the chemical topology and molecular complexity of therapeutic drugs. Systematic studies found an increase of the sp3-carbon fraction, e. g. saturated rings, as the compound progresses from hit to the status of a drug candidate in clinical phases2. The deferral of molecular complexity and difficult chemistry of sp3-carbons to the later stages of drug development may also defer the risk of failure to costly clinical trials.

In the present study, we utilized CrystalsFirsts SmartSoak® technology and performed a crystallographic screen of 200 fragments derived from natural products comprising a high fraction of sp3-carbons. The preliminary results show an extraordinary hit rate over 30 % that allows a wide spectrum of follow-up compounds using analogues-by-catalogues approach or by classic organic chemistry.

(1) Erlanson et al., Nat. Rev. Drug Discov. 2016, 15 (9), 605–619.
(2) Lovering et al., J. Med. Chem. 2009, 52 (21), 6752–6756.

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